Drug Monograph

A - Drug Name

goserelin

SYNONYM(S): ICI-118,630

COMMON TRADE NAME(S): Zoladex® (AstraZeneca); Zoladex® LA (AstraZeneca)

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B - Mechanism of Action and Pharmacokinetics

Goserelin is a synthetic analog of gonadotropin releasing hormone (GnRH/LHRH). Following initial stimulation of luteinizing hormone (LH) release and a transient elevation in serum testosterone and estradiol, chronic administration of goserelin results in inhibition of gonadotropin secretion, with castrate levels being achieved after 3-4 weeks

Absorption	Goserelin is rapidly absorbed following subcutaneous administration. Peak concentrations reached within 8-22 days and 24 hours, for the 3.6mg and 10.8mg dosage forms respectively. Bioavailability	Inactive orally
Distribution	Cross blood brain barrier?	No information found
	PPB	27.3%
Metabolism	Hydrolysis of the C-terminal amino acids into peptide fragments.	
	Active metabolites	None
	Inactive metabolites	Peptide fragments
Elimination	Mainly kidney (>90%), minor hepatic excretion.	

Urine	>90%; 20% unchanged
Half-life	4.2 hours (males), 2.3 hours (females)

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C - Indications and Status

Health Canada Approvals:

- Palliative treatment of hormone-dependent, advanced prostate cancer, stage M1 (TNM) or stage D2 (AUA) (3.6 and 10.8 mg formulations)
- In combination with a non-steroidal antiandrogen and radiation in locally advanced prostate cancer (stage T3, T4, or bulky stage T2b, T2c) (3.6 mg or 10.8 mg formulations)
- Adjuvant hormone therapy to external beam irradiation in locally advanced prostate cancer (stage T3-T4) (3.6 mg or 10.8 mg formulations)
- Palliative treatment of advanced breast cancer in pre- and perimenopausal women whose tumours contain estrogen and/or progesterone receptors (3.6 mg formulation only)
- Adjuvant therapy of early breast cancer in pre- and perimenopausal women whose tumours contain estrogen and/or progesterone receptors who are unsuitable for, intolerant to, or decline chemotherapy (3.6 mg formulation only)

Refer to the product monograph for other non-cancer indications approved by Health Canada.

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D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: None

The following table contains adverse effects reported in cancer patients.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia	E
	Arterial thromboembolism (1%)	E D
	Heart failure (5%)	D
	Hypertension (2%)	E

	Hypotension	E
	QT interval prolonged (rare)	D
	Venous thromboembolism (1%) (rare)	E D
Dermatological	Alopecia	E
	Rash (3%) (mild)	E
Gastrointestinal	Abdominal pain (1%)	E
	Anorexia (4%)	E
	Constipation (<1%)	E
	Diarrhea (12%)	E
	Nausea, vomiting (11%)	I
	Weight gain (2%)	E
General	Cysts (ovarian)	L
	Edema (5%)	E
	Fatigue (5%)	E
	Tumour flare (< 10%, may be severe)	I
Hematological	Myelosuppression (6%) (mild)	D
Hepatobiliary	↑ LFTs (1%)	E
Hypersensitivity	Hypersensitivity (rare)	I
Immune	Autoimmune disorder (lupus-like syndrome - rare)	E
Injection site	Injection site reaction (3%)	I
	Other - Injection site injury/vascular injury (rare)	I
Metabolic / Endocrine	Alcohol intolerance (rare)	E
	Glucose intolerance (<10%, may be severe)	E
	Hyperlipidemia	E D
	Other - Pituitary hemorrhage (rare)	E
Musculoskeletal	Arthralgia /myalgia (<1%)	E D
	Osteopenia (<10%, may be severe)	D
Nervous System	Dizziness (3%)	E
	Headache (rare)	E
	Insomnia (rare)	E
	Mood changes (or personality changes; <10%)	E
	Paresthesia (1%)	D
Ophthalmic	Glaucoma (rare)	E
	Other (Ocular symptoms - rare)	E

Renal	Renal failure	E
Reproductive and breast disorders	Androgen deprivation symptoms (or estrogen deprivation symptoms; 76%)	I E D
	Vaginal bleeding	L
Respiratory	Cough, dyspnea (4%)	E
Urinary	Urinary symptoms (12%)	E
Vascular	Hot flashes (76%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Transient increases in testosterone and estradiol may cause **disease flare** with urinary obstruction, spinal cord compression (in prostate cancer) and an increase in bone pain.

In non-orchidectomized patients, the initial stimulation of the pituitary caused by goserelin produces an acute increase in the concentration of testosterone, usually during the first week of treatment. This is accompanied by disease flare in <10% of patients. Increased bone pain and less frequently, neuropathy, symptoms of urinary tract obstruction (e.g. renal failure) and/or spinal cord compression (e.g. weakness of lower extremities) occur. Patients with metastatic vertebral lesions and/or with urinary tract obstruction should begin goserelin therapy under close supervision. Alternatively, cyproterone 100 mg bid, flutamide 250 mg tid, bicalutamide 50mg daily or nilutamide 150mg daily may be given concurrently with the first administration of goserelin in prostate cancer patients. Since the danger of a flare reaction abates in the second week following goserelin administration, there is no strong reason for continuing antiandrogens much beyond this time.

Serum estradiol suppression will induce **amenorrhea** generally within 8 weeks of starting treatment. Vaginal bleeding (due to estrogen withdrawal) of various duration and intensity may occur during early treatment, and is expected to stop spontaneously. If female patients continue to experience menstrual bleeding, estradiol levels should be measured; rule out intrauterine pathology if menstrual bleeding persists with estradiol at postmenopausal levels. Menses usually resumes within 8 weeks following completion of treatment at 3.6 mg q4w. Rarely, some women may become menopausal during goserelin treatment and do not resume menses upon cessation.

Long-term use results in **hypogonadism;** it is unknown whether this is reversible.

Bone loss may occur during the hypoandrogenic state caused by long-term use of goserelin. Risk factors such as older age, pre-existing osteopenia, family history of osteoporosis, chronic use of corticosteroids, anticonvulsants, or other drugs that may lead to osteoporosis or chronic alcohol/tobacco abuse should be carefully considered before starting treatment. Study data suggest that some recovery of bone mineral density may occur on cessation of goserelin. **Hypercalcemia** has been reported in prostate and breast cancer patients (with bone metastases) after starting

goserelin treatment.

Androgen deprivation may increase **cardiovascular risk** (MI, sudden death, stroke) in men with prostate cancer since it can adversely affect cardiovascular risk factors, such as increased body weight, reduced insulin sensitivity and/or dyslipidemia. **QTc prolongation** has been described and goserelin should be used with caution in patients with other risk factors such as congenital long QT syndrome, abnormal electrolytes and concomitant medications which prolong QTc. **Reduction in glucose tolerance** and increased risk of developing diabetes have been reported in men treated androgen deprivation therapy. **Anemia** is also a known physiologic effect of testosterone suppression.

There is an increased risk of **depression** in patients on GnRH agonist treatment. Worsening of depression, including suicidal attempts, have been reported.

Pituitary apoplexy has been reported rarely in patients using GHRH agonists, usually in patients with pre-existing adenomas. Most occurred within 2 weeks of the first dose, and some within the first hour. Symptoms include sudden headache, vomiting, visual changes, altered mental status and sometimes cardiovascular collapse.

Hypersensitivity reaction and anaphylaxis have been described. **Injection site injury and vascular injury** have been reported, including pain, hematoma, hemorrhage, and hemorrhagic shock requiring blood transfusions and surgical intervention. Caution should be taken during administration into the anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches.

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E - Dosing

Refer to protocol by which patient is being treated.

Adults:

Subcutaneous - To be injected into anterior abdominal wall

Breast Cancer:

- q28d: 3.6 mg

Prostate Cancer:

- q28d: 3.6 mg
- q3m (or q13 weeks): 10.8 mg

When given in combination with a non-steroidal antiandrogen and radiotherapy, goserelin should be started 8 weeks prior to radiation and continue until completion of radiotherapy. (e.g. Goserelin 3.6 mg SC 8 weeks pre-radiation, then followed by 10.8 mg SC 4 weeks pre-radiation)

Dosage with Toxicity:

Dosage with myelosuppression: No adjustment required.

Dosage with Hepatic Impairment:

No adjustment required.

Dosage with Renal Impairment:

No adjustment required. (Although half-life is longer in patients with CrCl < 20 mL/min, it is not likely to cause drug accumulation.)

Dosage in the elderly:

No adjustment required.

Children:

Safety and efficacy not established

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F - Administration Guidelines

- Subcutaneous injection of the depot into the anterior abdominal wall, below the navel line. Injection usually given at the Cancer Centre or physician's office. Drug supplied by outpatient prescription. Should be administered by a healthcare professional experienced in administering deep subcutaneous injections under the supervision of a physician,
- Store in original packaging between 2°C and 25°C. Protect from light and moisture.

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G - Special Precautions

Contraindications:

- patients who have a hypersensitivity to this drug or any of its components
- females with undiagnosed abnormal vaginal bleeding.

Other Warnings/Precautions:

- Use with caution in patients with osteoporosis (or risk factors for osteoporosis), diabetes, risk factors for QT prolongation, history of depression, cardiovascular disease, metastatic vertebral lesions and/or urinary tract obstruction due to the risk of disease flare.
- Patients who experience anaphylaxis/anaphylactoid shock while on goserelin may require removal of the implant. If implant removal is necessary, it may be located by ultrasound.
- Goserelin requires administration by deep subcutaneous injection and is not recomended in patients with low body mass (BMI <18.5) or in patients who are fully anticoagulated (INR >2).

Other Drug Properties:

- Carcinogenicity: No

Pregnancy and Lactation:

- Genotoxicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Not recommended for use in pregnancy. Adequate non-hormonal contraception must be used by both sexes during treatment and for at least 6 months after goserelin cessation (general recommendation).
- Breastfeeding: Not recommended
  Goserelin is secreted into milk in animals.
- Fertility effects: Fertility may be affected in males and females, but may be reversible.

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H - Interactions

Suppression of pituitary-gonadal system by GnRH may interfere with diagnostic tests of pituitary-gonadal function.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of QT prolongation	Additive effects with androgen deprivation	Caution

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Blood glucose/HbA1c levels	Baseline and periodical, especially in diabetic patients
EKG, Electrolytes, (including K, Ca, Mg)	Baseline and periodic for at risk patients
PSA (if applicable)	Baseline and periodic
Clinical assessment of disease flare, local reactions, thromboembolism, cardiovascular effects, osteoporosis, psychiatric effects, hot flashes, signs of abdominal hemorrhage	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

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K - References

Goserelin: AHFS Drug Information. Accessed http://www.ahfsdruginformation.com on September 12, 2014.

Product Monograph: Zoladex® and Zoladex® LA (goserelin). AstraZeneca Canada Inc., October 22, 2015.

Product Monograph: Eligard® (leuprolide). Sanofi-aventis Canada Inc. May 31, 2011.

March 2016 updated adverse effects, special precautions and monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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